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PROPOSED EMERGENCY EXPOSURE LIMITS FOR MONOMETHLYHYDRAZINE

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The experiments reported herein were conducted according to the "Guide for Laboratory Animal Facilities and Care," 1965 prepared by the Committee on the Guide for Laboratory Animal Resources, National Academy of Sciences—National Research Council; the regulations and standards prepared by the Department of Agriculture; and Public Law 89–544, "Laboratory Animal Welfare Act," August 24, 1967.

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13. ABSTRACT

Current EEL values for monomethylhydrazine (MMH), a rocket propellant, have been based on minimal information consisting primarily of acute effects. The acute effects of MMH are seen only at lethal or supralethal dose levels and consequently a series of experiments were conducted to define an atmospheric concentration of MMH which would produce no irreversible injury and no clinical evidence of central nervous system (CNS) injury. Dogs, monkeys, rats and mice were exposed to MMH vapors for periods of 15, 30, and 60 minutes to concentration x time (CT) doses of 900 ppm-minutes. The 900 ppm-minute CT dose of MMH, which was 25% of the LC_0 concentration for the most susceptible animal species tested, included a safety margin below the lowest dose reported to produce marginal decrement of performance in trained cats and monkeys. In view of the negative finding in all species exposed to the 900 ppm-minute CT dose level of MMH, we recommend an upward revision of current emergency exposure limits (EEL) values.

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FOREWORD

This is one of a series of technical reports describing results of the experimental laboratory programs being conducted in the Toxic Hazards Research Unit. This report is concerned with research conducted to define safety limits for emergency exposures to monomethylhydrazine (MMH) vapors. These emergency exposure limits (EEL's), are intended for use as engineering design safety guide lines to limit maximum accidental human exposures to MMH.

The experimental program has been accomplished by SysteMed Corporation (Newport Beach, California) under Contract F33615-67-C-1025 for the Toxicology Branch, Toxic Hazards Division, Aerospace Medical Research Laboratory, Wright-Patterson Air Force Base, Ohio. The contract was initiated in support of Project 6302 "Toxic Hazards of Propellants and Materials," and Task 01, "Toxicology," Work Unit No. 008. K. C. Back, Ph. D., is the technical contract monitor for the Aerospace Medical Laboratory. The research described in this report was conducted over an 11-month period from November 1967 through October 1968.

J. D. MacEwen, Ph. D. is the principal investigator for the contractor in the conduct of the research program. Acknowledgement is made to M. S. West and L. C. DiPasquale for technical assistance in conduct of the animal exposures and to W. F. MacKenzie, Major, USAF, VC and P. N. Monteleone, Major, USAF, MC for pathologic evaluation of experimental animals. Additional pathology studies were conducted by R. L. Patrick, M. D. of the Laboratory for Experimental Biology, St. Louis, Missouri.

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This technical report has been reviewed and is approved.

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SECTION I

INTRODUCTION

Monomethylhydrazine (MMH) is a fuel used in rocket propulsion systems and consequently represents an exposure hazard to fuel manufacturing and handling personnel. The investigation of MMH toxicity has been a subject of great interest although the major research emphasis has been placed upon oral, intravenous, and percutaneous introduction of this chemical agent at lethal or supralethal dose levels. The comparative toxicities of hydrazine, UDMH, SDMH, and MMH were reported by Witkin (reference 1) in 1956. Witkin demonstrated that there was little difference in toxicity between the compounds when administered by the oral, intravenous and intraperitoneal routes. The principle action of the hydrazines was effected upon the central nervous system producing severe convulsions resulting in death. Reynolds and Back (reference 2) reported decreased performance in trained primates at subconvulsant doses of MMH (2.5 mg/kg). The performance decrement appeared prior to or in the absence of clinical signs of MMH intoxication. Similar changes in the learned performance of cats have been reported by Sterman et al (reference 3).

Acute inhalation studies of MMH toxicity have been reported for four animal species (dog, monkey, rat and mouse) by Haun (reference 4) and others (reference 5). The pertinent findings of these studies conducted at near lethal atmospheric concentrations form the basis for the EEL studies.

A consistent finding in the nonfatal exposure of dogs to concentrations of MMH at or near the approximate LC_{50} value was a transient hemolytic anemia characterized by significant decreases in hematocrit, red blood cells, and hemoglobin which continued for several days postexposure. The destruction of red blood cells was accompanied by an increase in reticulocytes during the period of maximum decline in hematocrit levels. The process of recovery was complete within 30 days postexposure at which time normal values of the affected blood parameters were observed. Small groups of Macaca mulatta monkeys were exposed to MMH to determine their response relative to the squirrel monkeys previously exposed. On the basis of results from one-hour exposure periods, and in view of the finding that other species have shown a rather predictable response to a CT (concentration x time) gradient, Rhesus monkeys are more resistant to the acute effects of MMH than either the squirrel monkey or the dog. One-hour exposures to concentrations at or above 170 ppm proved lethal, whereas exposures ranging from 120-160 ppm did not; this response places the Rhesus monkey between the rat and the mouse in susceptibility to MMH. An approximate one-hour LC_{50} of 162 ppm MMH was determined for this species.

Exposure of Rhesus monkeys to maximal nonlethal concentrations of MMH has shown that the typical hematologic response exhibited by dogs is not demonstrated by this subhuman primate; there is but slight evidence of the anemia previously described for dogs. This finding is in agreement with reported studies on the effects of injected monomethylhydrazine (reference 6) which have shown that erythrocyte hemolysis in the monkey is minimal (approximately 10% reduction of RBC's with rapid recovery).

A common gross pathologic finding in all species, following lethal exposures to MMH, was pulmonary congestion with some hemorrhage, hepatic congestion of varying degree, and swelling of the renal tubular epithelium which was frequently glassine and eosinophilic in appearance. In large animals, whose brain tissues were examined, subarachnoid hemorrhage was frequently observed. This response was probably related to the severe convulsions observed, as was the consistent finding in dogs of remarkably bloodless spleens in which the sinusoids were virtually empty. In some cases, the splenic smooth muscle bundles appeared thickened and contracted.

The amount of visceral congestion and hemorrhage observed was not sufficient to produce death and could only be attributed to CNS damage as previously reported by Jacobson et al (reference 5).

In animals that survived near lethal exposures to MMH and were killed serially over a period of approximately 60 days postexposure, the visceral congestion was still apparent although not as severe as in those animals that died during exposure. The most common and persistent finding, however, was renal damage which ranged from mild swelling of the tubular epithelium to vacuolization and coagulative necrosis of those epithelial cells.

The primary purpose for the investigation and definition of MMH LC_{50} values was to form some basis for subsequent studies designed to assist in the interpretation of emergency exposure limits (EEL) for man. The basic philosophy pertaining to Short-Term Limits and Emergency Exposure Limits (EEL's) for inhalation of toxic substances has been frequently discussed by others (references 7 through 9) and will not be reiterated here. Very briefly, however, the term 'EEL' refers to a "single event" limited exposure which is not expected to incapacitate sufficiently to prevent escape. Such an exposure would be one where the occurrence was possible but unpredictable, and where an individual so exposed would not encounter the substance again until careful study indicated either no injury or, in the event of injury, a complete recovery. Emergency inhalation exposures, therefore, are not to be associated with acceptable concentrations in a work environment atmosphere.

EEL's currently in use for MMH are 3, 7, and 10 ppm for 60, 30, and 10 minutes, respectively. On the basis of animal response to acute MMH exposures, and in view of the purpose for recommendation of EEL's, it appeared that higher values for MMH might have been warranted. Some experimentation was necessary for clarification of this point and, accordingly, was conducted by the Toxic Hazards Research Unit.

SECTION II

MATERIALS AND METHODS

EXPERIMENTAL RATIONALE

The rationale for the conduct of experiments to define safe emergency exposure limits was based on data obtained from previous acute toxicity studies. The plot of LC_{50}'s for each of four animal species tested is shown in figure 1. Plots of MMH concentration versus time permit extrapolation of the best fit lines through the respective LC_{50} values and yield a theoretical straight-line dose-response for each species. Thus, from a theoretical viewpoint, two rodent species (rats and mice) exposed continuously to 3.5-5 ppm of MMH would exhibit a 50% lethal response following approximately one week of exposure, whereas beagles and squirrel monkeys given this exposure would show 50% response at approximately one day (24 hours). Preliminary experiments with Rhesus monkeys, however, indicated a response midway between that shown for mice and for rats. The squirrel monkeys, therefore, represent the most susceptible species tested.

It is well known that the plot of theoretical values cannot be considered as a true dose-response relationship; the reactivity of MMH and the body defense mechanisms undoubtedly negate such an empirical response. Even so, the straight-line plots shown in figure 1 should represent the maximum possible response.

In this context, then, experiments were designed to indicate the validity of recommended EEL's for MMH. Current EEL's are shown as point plots in figure 1. Note that a straight-line dose-time relationship has not been recommended. If this had been applied, however, the 10-minute EEL would have been set at approximately 30 ppm of MMH rather than at the currently suggested 10 ppm.

The MMH concentrations selected for EEL testing on the four selected species (rat, mouse, beagle dog, and Rhesus monkey) were based on a CT of 900 ppm-minutes. This CT value was approximately 25% of maximum nonlethal concentrations for the most susceptible species, the squirrel monkey, and was also five times higher than the current EEL values adopted by the NAS-NRC Advisory Center on Toxicology. The selected concentrations were 15, 30, and 60 ppm MMH for single exposure periods of 60, 30, and 15 minutes respectively.

EXPERIMENTAL ANIMALS

Rodents

Groups of 18 Sprague-Dawley rats (140-175 grams) and 18 ICR (Swiss origin) mice (25-30 grams) were exposed to the 900 ppm-minute dose of MMH

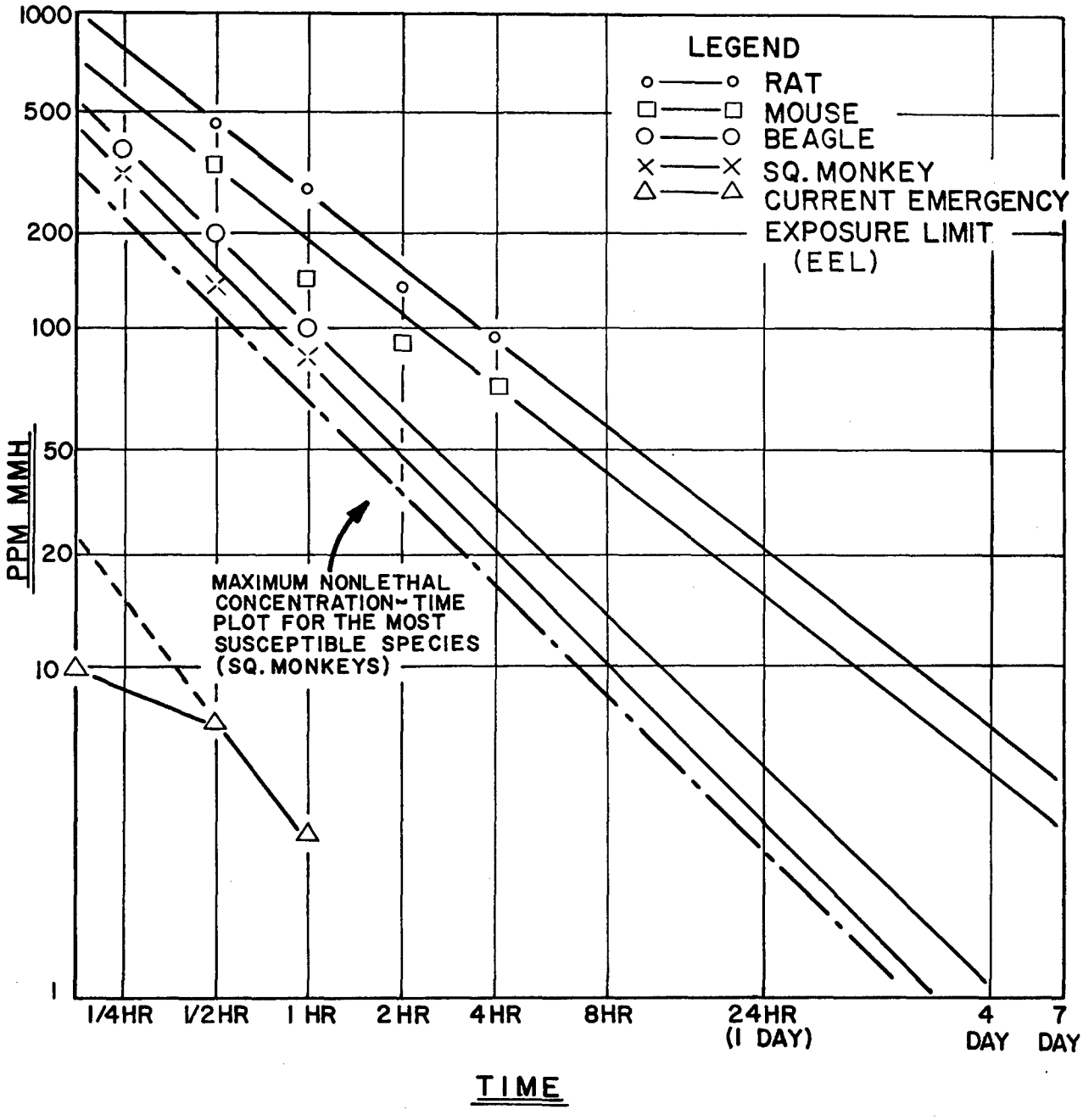

Figure 1

Acute Toxicity of Monomethylhydrazine

(MMH)

LC_{50} Values of Four Species

vapor for 15, 30, and 60 minute periods. Groups of 9 unexposed control rodents were used for comparison with each test group. Additional groups equal in size and number, were subjected to higher time-concentration exposures; namely, 150, 75, and 40 ppm MMH for 15, 30, and 60 minutes respectively.

The rats were weighed before exposure and at 1, 3, and 7 days postexposure. One third of the exposed and control rodents were killed at 1, 3, and 7 days respectively for evaluation of possible injury and reversibility. During the postexposure period all animals were fed ad libitum.

Dogs and Monkeys

Thirty-two purebred female beagle dogs (6 to 9 months old) were exposed in groups of 8 to each of the 900 ppm-minute test combinations. Postexposure observations were made for a period of 30 days on 2 MMH exposed and 2 control dogs for each CT group while the remaining dogs were killed at 1, 3, and 7 days for pathology evaluation. The groups of dogs held throughout the 30-day postexposure observation period were examined clinically and routine blood tests were made twice weekly. Necropsies were performed at the end of the observation period and tissue specimens were submitted for histopathology.

Comparable numbers (32) of female monkeys (Macaca mulatta) weighing 3 to 5 kilograms were exposed to the same time-concentrations of MMH as were the dogs. Again most monkeys were killed at 1, 3, and 7 days postexposure for pathologic evaluation and groups of 2 monkeys exposed to each MMH CT level tested were observed clinically for 30 days after which necropsies were performed and histopathology evaluations conducted.

EXPOSURE CHAMBERS

Rodent exposures were conducted in small glass chambers (bell jar) as described by Haun (reference 4). The animals were placed in one of a pair of chambers with air passing through it. The desired MMH concentration was established in an adjoining empty chamber and then the entering and exhaust air streams were simultaneously switched by means of valves and the exposure begun.

Dogs and monkeys were exposed in a standard Rochester Chamber with MMH introduced into the air supply in the usual manner.

An infusion pump was used to meter the correct quantities of MMH at the desired delivery rate for each exposure. An adjustable syringe cradle was constructed to firmly hold a 5, 10 or 20 cc syringe, making it possible to use the apparatus in a vertical rather than in the normal horizontal position. A smaller version of the evaporator unit described by Carpenter et al (reference 10) was used to vaporize the MMH. Fresh supplies of MMH were used for each exposure to prevent the use of partially oxidized material. The vapor generation equipment was located in a small hood to prevent exposures to research personnel.

ANALYTICAL METHOD

Because of the reactive nature of MMH and the extremely small range of concentrations between the no-effect and effect levels seen in the preliminary experiment, a method of continuous analysis was required. The continuous monitoring of chamber MMH concentrations was accomplished by use of an electron capture instrument (reference 11) which measured the concentration of an aerosol formed by the reaction of MMH with trifluoroacetic acid vapor.

This instrument is a self-contained monitoring system suitable for continuous analysis, in the parts per billion range, of acidic or basic vapors which can be reacted to form aerosols within the apparatus. An electrical signal generated by the electron capture detector was transmitted to a millivolt recorder. Typically, the instrument recorder response time was only 12 seconds, permitting almost instantaneous readout of chamber concentrations.

The automatic MMH analyzer was calibrated daily using standards made in polyester film bags filled with 200 liters of dry nitrogen into which the desired amount of liquid MMH was injected through a rubber septum. Gentle warming and manipulation of the bag insured complete evaporation and mixing. The extreme sensitivity of the electron capture instrument made it necessary to predilute the chamber samples with room air before analysis could be made.

Sampling from different positions in both Rochester and bell jar chambers showed that MMH concentrations were uniform throughout. During exposures, samples were taken from a point as near the animal breathing zone as possible. The sampling probe was movable and could be relocated if necessary to prevent animal interference with air flow.

SECTION III

EXPERIMENTAL RESULTS

No significant differences between MMH exposed and control rodents were observed at any of the six selected EEL test concentrations. The mean pre- and postexposure weights of the MMH exposed rats and their controls are summarized in table I. The three individual groups of the 2250 ppm-minute and 900 ppm-minute CT exposures have been lumped together since there were no significant differences between them. Organ to body weight ratios are presented in table II for the same groups of animals. Again, no significant differences were observed at either the 900 ppm-minute or the 2250 ppm-minute dose levels.

No effects on body weight were observed in either dogs or monkeys exposed to three 900 ppm-minute MMH exposure systems. At necropsy both species exhibited mild transitory changes which consisted of minimal congestion with slightly increased pigmentation of the renal cortex. These changes had completely resolved by the 30-day sacrifice period.

Histopathologic evaluation of tissues of both dogs and monkeys necropsied at 1, 3, 7, and 28 days postexposure showed no significant differences from control animals. Mild pulmonary congestion was seen in some dogs on the third postexposure day but this is not believed to be related to the MMH exposure. It was not seen in animals necropsied at subsequent postexposure periods. An additional group of dogs exposed to 15 ppm MMH for one hour for evaluation of clinical chemistry parameters was also negative with respect to pathologic effects.

No clinical signs or symptoms of CNS changes could be observed in any of the four animal species exposed to MMH in the EEL test series. There was also no indication of respiratory irritation as had been observed during MMH inhalation exposures near the LC_{50} concentration.

Biochemical determinations on blood specimens taken from the dogs and monkeys exposed to the three concentration time periods remained within normal ranges, with the exception of glucose values. The drop in postexposure glucose values was believed to be an analytical error in the enzyme method due to a rise in laboratory temperature which resulted from construction activities. Consequently, an additional series of five dogs each were exposed to MMH concentrations of 15 ppm and 8 ppm for a 60-minute period. Baseline values were collected on all dogs for 4 weeks prior to the MMH inhalation exposure. These MMH exposed dogs and their controls were tested twice weekly for 7 weeks postexposure. Composite weekly mean values for the blood glucose levels are listed in table III. There were no significant differences between the exposed dogs and their controls.

TABLE I

MEAN BODY WEIGHTS OF ALBINO RATS
EXPOSED TO MONOMETHYLHYDRAZINE
(weight in grams)

	Days Postexposure				No. of
	0	1	3	7	Rats
Exposed: CT = 2250	153	155	166	196	54
Controls	148	155	169	197	27
Exposed: CT = 900	163	167	180	203	54
Controls	163	170	182	205	27

TABLE II

MEAN ORGAN TO BODY WEIGHT RATIOS OF ALBINO RATS
EXPOSED TO MONOMETHYLHYDRAZINE
(organ weight/100 gram body weight)

	Heart	Lungs	Liver	Spleen	Kidney	No. of Rats
Exposed: CT = 2250	0.408	0.695	4.391	0.438	0.950	54
Controls	0.397	0.662	4.537	0.428	0.940	27
Exposed: CT = 900	0.426	0.667	4.638	0.416	0.938	54
Controls	0.406	0.656	4.583	0.408	0.924	27

TABLE III

BLOOD GLUCOSE LEVELS IN MMH
EXPOSED DOGS AND THEIR CONTROLS

	Weekly Period	Glucose mg/100 ml		
		Exposed CT = 900	Exposed CT = 450	Controls
Pre-Exposure	1	99	101	101
	2	101	101	107
	3	99	95	103
	4	107	107	112
Post-Exposure	1	106	106	110
	2	107	106	109
	3	103	104	106
	4	103	105	108
	5	98	99	105
	6	100	99	103
	7	98	104	102

SECTION IV

DISCUSSION AND RECOMMENDATIONS

An important factor in considering establishment of inhalation exposure limits for MMH is its rapid oxidation in air and in the animal. Air oxidation begins immediately and is relatively complete within one hour as reported by Vernot et al (reference 12). The primary oxidation products of MMH in air are methane and nitrogen. Small amounts of other carbon containing compounds are also formed which include CO_2. Dost et al (reference 13) have described the metabolic fate of MMH in rats using ^{14}C labeled material injected intraperitoneally. The in vivo oxidation of MMH reaches a maximum rate within two hours and is essentially complete 3-4 hours postinjection. Approximately 30% of the metabolized MMH is excreted as methane and about 10% as CO_2. The bulk of the remaining carbon containing metabolite appears in the urine.

These findings on the metabolic fate of MMH with respect to rate of decomposition agree with the reported findings of Reynolds and Back (reference 2). The performance decrement induced in primates by MMH began 1-2 hours after injection and decreased significantly 4-5 hours after injection.

The induction of performance decrement in primates required an MMH dose of 2.5 mg/kg. Calculation of the maximum possible inhaled dose of MMH in the studies reported herein show it to be 0.5 mg/kg for the primate or 20% of the dose required for performance decrement.

In view of the negative findings in all species from MMH inhalation exposures of 900 ppm-minutes and in both rats and mice at 2250 ppm-minutes and the safety factor for performance decrement, we recommend an upward revision of the Emergency Exposure Limit values for monomethylhydrazine as shown below:

Minutes	PPM MMH
10	90
30	30
60	15

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